Health Consequence Scoring for Contaminants in Animal Feed

I. Introduction

A. Overview

The goal of CVM's Animal Feed Safety System (AFSS) is to develop and implement a comprehensive, risk-based, preventive animal feed safety system that minimizes, reduces or eliminates the risks to animal and human health that can arise from animal feed. An integral part of this effort is the development of a relative-risk ranking method for all potentially toxic or deleterious biological, chemical and physical hazards in animal feed.

It is very important to note that this risk-ranking exercise is not intended for the estimation of risks associated with any one feed contaminant; instead, it is intended to be a tool for ranking of the relative risks of feed contaminants to aid FDA in setting priorities for allocating its resources in a risk-based manner.

B. Risk

Risk assessment may be thought of as answering four basic questions:

1. What can go wrong? (Hazard Identification);
2. What are the consequences? (Consequence Assessment or Hazard Characterization);
3. How can it happen? (Exposure Assessment); and
4. What is the likelihood it would go wrong? (Risk Estimation).

To address the first question, or the Hazard Identification step, the AFSS has compiled a list of feed contaminants that are the initial focus of the risk-ranking exercise. The second step is the assessment of the health consequences associated with the identified hazards. These two steps are the subjects of this document and the September 12, 2006 AFSS public meeting.

Questions 3 (Exposure Assessment) and 4 (in which the Consequence and the Exposure Assessments are combined to estimate relative risks) will be the subjects of future AFSS documents and public meetings.

C. Health Consequence Scoring

The purpose of this document is to provide a brief overview of the risk-ranking approach with primary focus on methods used to determine Health Consequence Scores (HCS). Two factors contribute to the HCS:

1. Likelihood of illness (if animals are exposed to the hazardous agent, how likely is it that they will be adversely affected?), which also may be expressed as the potency of the hazardous agent (the amount of the hazardous agent required to cause the adverse effect). For the AFSS, this factor is represented by the Potency Score (PS).

2. Severity of the illness (if animals are adversely affected, how severe is the effect?); e.g., death v. vomiting v. reduced feed consumption. For the AFSS, this factor is represented by the Severity Score (SS).

Scores will be developed on a species basis (humans, dogs, pigs, etc.) and on an exposure basis (acute and chronic). Data used in the HCS process are reviewed for quality to ensure that they are at least minimally adequate according to standard criteria. It is likely that, for the majority of the hazards, derivation of HCS will require that relevant data in one animal species be extrapolated, with the use of appropriate safety factors, to other species for which data are not available. Further, for those agents where the data are insufficient to specify the nature of the agent, we may choose a ranking based on a worst case (a "health-protective" or conservative) assumption. In all cases, extrapolations and assumptions that are used in the scoring process will be clearly documented.

It is important to remember that this is an iterative process and the relative rankings of individual hazardous agents will be revisited, as necessary based on available data.

II. Chemical Contaminants

A. Acute Effects

Acute effects are those effects that occur following a single or short-term exposure to a toxic dose of a chemical. These effects may be easily observed by both trained and untrained observers, in the case of death, seizures, or gastrointestinal illness such as vomiting, or may be only identified upon laboratory examination of affected tissues and organs after the exposure has occurred.

Given that chemicals may cause different toxic effects (e.g., liver effects vs. kidney effects), comparing the toxicity of chemicals is difficult unless a common toxicological endpoint is used. One measure of acute toxicity is the LD_{50}[1] test. It is probably the most common acute toxicity test performed on chemicals that may be consumed, inhaled or touched by animals and humans. The LD_{50} is the amount of a chemical given in a single dose (the Lethal Dose, usually measured in mg chemical per kilogram of body weight of the test animal) which causes the death of 50% of a group of test animals. Most LD_{50} and other acute toxicity tests are conducted in rodents. For determining acute effects of chemical contaminants in animal feed, oral LD_{50} results are more relevant than inhalation or dermal LD_{50} results.

To incorporate information from studies other than LD_{50} reports, a weight-of-the-evidence approach will be used to assign the appropriate potency or severity score, based on information for chemicals of related chemical and physical properties, or with similar reported toxicity profiles.

[1] The classical LD50 test is not required by FDA for determining safety, and its use is not part of agency testing policy. The FDA's full policy regarding the LD50 test is described in the Federal Register of October 11, 1988 (53 FR 39650).

1. Acute Health Consequence Scoring

The Acute Health Consequence Score (C_A-HCS) for each chemical contaminant is calculated by multiplying the contaminant's Acute Potency Score (C_A-PS) by its Acute Severity Score (C_A-SS).

a) Acute Potency Scoring

The majority of available information on the ability of chemical feed contaminants to cause acute effects (potency) is data from LD_{50} studies. Thus, the C_A-PS is primarily determined by the range of LD_{50} values for the contaminants placed on a comparative scale, which is divided into 3 categories. The first category are those chemicals with the highest LD_{50}s (the lowest potency), which are given a score of 1. The second category is for chemicals with mid-range LD_{50}s (medium potency), given a score of 2. The third category is for the high potency chemicals (low LD_{50}s), which are assigned a score of 3. For those chemicals with more than one reported LD_{50} value, the lowest value is used.

b) Acute Severity Scoring

The C_A-SS is a numerical score assigned to a chemical based on the types of effects observed in acute toxicity studies or other data sources. From least to most severe, categories of acute effects for the AFSS relative risk model are:

- No adverse effects at the highest dose tested;
- Adverse effects other than those noted below;
- Neurotoxic or neurobehavioral effects;
- Death.

A C_A-SS is assigned to each chemical based on the most severe (or worst) effect observed in all studies used to assess the acute toxicity of the chemical.

B. Chronic Effects

Chronic chemical effects are those health effects that occur when a chemical is consumed repeatedly (e.g., every day) for a long period of time, often for the majority of the animal's or human's lifetime. The two primary sources of information on the chronic effects resulting from exposure to a chemical are from long-term studies on humans (epidemiology studies) and laboratory animals (chronic toxicity tests). For animal feed chemical contaminants, the majority of the available data are from laboratory animal studies that can be classified as chronic studies, as follows:

- Chronic toxicity studies (daily exposures to the test chemical for periods ranging from more than 90 days to 2 years in typically used laboratory animals);
- Carcinogenicity studies (daily exposures for the lifetime of the test animal – usually rodents);
- Reproductive toxicity studies (daily exposures focusing on the reproductive cycles of the test animals);
- Developmental toxicity studies (daily exposures focusing on the developmental cycles of the test animals).

Although it may be possible to characterize the chronic toxicity of a chemical using fewer or shorter studies than the ones listed, there is likely to be more uncertainty associated with such an estimate.

1. Chronic Health Consequence Scoring

The Chronic Health Consequence Score (C_C-HCS) for each contaminant is calculated by multiplying the contaminant's Chronic Potency Score (C_C-PS) by its Chronic Severity Score (C_C-SS).

a) Chronic Potency Scoring for Effects Other Than Cancer

For comparative purposes, the basis for the C_C-PS is an estimate of an Acceptable Exposure Level (AEL) for each chemical contaminant. The AEL is an estimate of the amount of a chemical (expressed on a body weight basis) that can be ingested daily over a lifetime that is likely to be without an appreciable risk of adverse effects, and is entirely analogous to EPA's reference dose (RfD) or FDA's Acceptable Daily Intake (ADI). The AEL will be determined according to the standard methodology used for RfD or ADI derivations; i.e., identification of the lowest NOEL or NOAEL (No Observed Effect Level or No Observed Adverse Effect Level), followed by applications of appropriate safety/uncertainty factors. The lowest AEL established for a contaminant is used to determine the C_C-PS.

The C_C-PS is determined by placing the AELs for all the contaminants on a comparative scale, which is divided into 3 categories. The first category is for those chemicals with the highest AELs (the lowest potency), which have a score of 1. The second category is for chemicals with mid-range AELs (medium potency), given a score of 2. The third category is for the high potency chemicals (low AELs), which are assigned a score of 3.

b) Chronic Potency Scoring for Cancer Effects

One measure of the potency of chemicals known or suspected of causing cancer is the estimated dose associated with a one-in-one-million increased lifetime risk of cancer. This estimated dose serves as a means to establish the relative potency of cancer-causing chemicals among each other, as well as a way to compare the potencies of cancer- and non-cancer causing chemicals.

For those cancer-causing chemicals without estimates of a one-in-a-million risk dose, a weight-of-the-evidence approach will be used to assign an appropriate potency category, based on analyses by various regulatory bodies and information for chemicals of related chemical, physical or toxicological properties.

c) Chronic Severity Scoring

The C_C-SS is a numerical score assigned to a chemical based on the types of effects observed in chronic toxicity studies or other data sources. From least to most severe, categories of chronic effects for the AFSS relative risk model are:

- No adverse effects at the highest dose tested;
- Adverse effects other than those noted below;

- Neurotoxic or neurobehavioral effects;
- Reproductive or developmental effects observed in the absence of significant maternal toxicity;
- Tumors observed and the chemical was determined to be a carcinogen under the conditions of the study, or the chemical has been determined to be a likely human or animal carcinogen;
- Death.

A C_C-SS is assigned to each chemical based on the most severe (or worst) effect observed in all studies used to assess the chronic toxicity of the chemical.

III. Biological Contaminants

The overall approach to Health Consequence Scoring for biological contaminants (B-HCS) is similar to that for the chemical contaminants, with both likelihood and severity of illness serving as the basis for the HCS. However, there are significant differences in the available data for biological and chemical contaminants: 1) the majority of the data on biological contaminants are derived from human studies that generally involve relatively less controlled exposure scenarios than the animal studies that form the basis for most of the chemical contaminant data; 2) the intricate relationship between a biological contaminant, the host's immune response and environmental factors makes it more difficult to interpret illness data; 3) illness data associated with biological contaminants may be attributed to unique factors and/or toxins (virulence factors) that are essential for infecting host cells and causing disease, and 4) some biological contaminants are host adapted and only infect certain animal species, while others are able to infect more than one animal species.

In order to maximize the use of available data, a weight-of-the-evidence approach will be used to determine HCS for biological contaminants. Data that are of a different nature than what is described in the scoring system below will be incorporated into the scoring process based on established principles of relative severity or relative potency of biological contaminants.

A. Biological Health Consequence Scoring

The Biological Health Consequence Score (B-HCS) for each biological contaminant is calculated by multiplying the contaminant's Biological Potency Score (B-PS) by its Biological Severity Score (B-SS).

1. Biological Potency Scoring

The two primary factors that compose the Potency Score for biological contaminants (B-PS) are the Median Effective Dose (MID) and the Infective Dose Range (IDR), where B-PS = MID x IDR:

The MID is the dose of the biological contaminant that results in infections; this is determined from published literature. The MIDs for all of the contaminants are placed on a comparative scale, which is divided into 3 categories. Each category is assigned a score as follows: those biological contaminants with the highest MIDs (lowest potencies) will have a score of 1; those with mid-range MIDs (medium

potencies) will have a score of 2; and those with the lowest MIDs (highest potencies) will have a score of 3.

The IDR is the range of infective doses reported in the published literature for a particular biological contaminant. The potencies associated with these ranges are scored in a manner similar to that used to score MIDs, in which a scale of 1 to 3 is used, where 3 represents the smallest range of infective doses, 2 represents a middle range of infective doses, and 1 represents the largest range of infective doses.

For some biological contaminants, the MID or the IDR may not be available to help determine the B-PS. In this situation, other data that may provide information on the potency of biological contaminants include morbidity and mortality rates. These data will be used to help establish the relative potency of biological agents without MID and IDR data by comparing them to biological agents with both MID data and morbidity/mortality information.

2. Biological Severity Scoring

The Severity Scores for biological contaminants (B-SS) are based on an analysis of the reported signs and symptoms for each biological agent, as follows:

A list of major signs and symptoms associated with biological disease agents will be developed by combining the signs and symptoms caused by each biological contaminant contained in the list of biological contaminants in feed. Each major sign and symptom will be assigned a severity score ranging from 1 to 5, with a higher number indicating a more severe sign or symptom. Mean severity scores for each major sign and symptom will be determined by averaging scores assigned to each sign and symptom by several experts. For example, if abortion in swine is assigned scores of 4, 2, and 3, respectively, by three experts, the mean sign score for abortion would be 3, that is, $(4+2+3) \div 3 = 3$.

For each biological contaminant, the overall severity score will be the sum of the mean severity scores for each sign and symptom exhibited by a person or animal species exposed to the biological contaminant.

Other data that may provide information on the severity of illness caused by biological contaminants include the percentages of persons or animals exhibiting each sign and symptom. These data may be combined with the signs and symptoms scoring data described above, where appropriate.

IV. Physical Contaminants

(To be added at a later date)